Statistical approaches to understanding the external validity of randomised control trials to target clinical populations: protocol for a systematic review (Version 1, 28 Sep 2020)

Contact

Mike Bradburn
m.bradburn@sheffield.ac.uk
University of Sheffield

Dr Daniel Hind
d.hind@sheffield.ac.uk
University of Sheffield

Faith Solanke
fsolanke1@sheffield.ac.uk
University of Sheffield

Contributions of Protocol Authors

Mike Bradburn and Daniel Hind conceived the review. MB, DH and Faith Solanke designed the review. FS was primarily responsible for the acquisition of the data. MB, DH and FS analysed and interpreted the data.

MB, DH and FS drafted the review and revised it critically for important intellectual content.

MB, DH and FS gave final approval of the version to be published.

MB, DH and FS agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Guarantor of the review
Mike Bradburn.

Introduction
Concern about the external validity of randomised controlled trials goes back to at least 1938, when Frank Yates and William Gemmell Cochran wrote:

“At present it is usually impossible to secure a set of sites selected entirely at random. An attempt can be made to see that the sites actually used are a "representative"

selection, but averages of the responses from such a collection of sites cannot be accepted with the same certainty as would the averages from a random collection."[1]

A common criticism of the statistical / epidemiological approach to controlled experiments is that the prioritisation of internal validity comprises external validity,[2] although other categories of ostensibly "real world" data clearly suffer the from same problem.[3,4] Nonetheless, overviews do consistently show that only RCTs are only externally valid in 30% of published empirical evaluations.[5,6] Likely sources of generalisability bias are overly restrictive research protocols,[7] particularly in pursuit of signal-to-noise ratio maximisation in explanatory research produced for regulatory purposes,[8,9] and the particularity of small studies.[10,11]

While the past decade has seen a growth in empirical studies evaluating the external validity of trials in particular settings,[6,12–19] few of these evaluate attempts to formally weight the results of RCTs using population data and methods more complicated than descriptive statistics.[6]

Aim

The aim of this review is to describe statistical methods for assessing the external validity of randomised control trials. This will be a rapid methodological review using formal and informal search strategies.

Specific Objectives

A description of statistical methods that are currently used to assess the external validity of randomised control trials.

A description of the contexts in which those statistical methods have been applied.

Methods

Eligibility Criteria

- Sources containing statistical methods to assess external validity of randomised controlled trials;
- Published material;
- Material comparing one or more randomised controlled trial with one or more reference cohort (e.g healthcare databases, population census);
- Statistical methods in sources must both: (i) compare at least one baseline characteristic of RCT participants to those of the reference cohort; and, (ii) re-estimate the treatment effect from the original RCT analysis.

Exclusion criteria

- Sources not available in English;
- Discursive sources detailing methodology without applied case studies.

Information Sources

British Educational Index and the Education Resources Information Center (ERIC) via EBSCO, as well as MEDLINE via Ovid.

We will not attach a date restriction to our searches

Search Strategy

We will use key papers already known to the review team to identify key terms for our search strategy. We plan to use the search strategies outlined below.

MEDLINE search strategy
1. "External validity".mp.
2. generali*ab*.mp.
3. or/1-2
4. *Randomized Controlled Trials as Topic/
5. Randomi*.ti.
6. or/4-5
7. 3 and 6

British Education Index and ERIC via EBSCO
S1 AB Random*
S2 AB Experiment*
S3 S1 OR S2
S4 SU Generali*
S5 AB external validity
S6 S4 OR S5
S7 S3 AND S6

We will also check the reference lists of eligible citations for further studies.

Data collection and management
Data abstraction processes will be piloted before the review. Citations will be downloaded into Mendeley reference management software to aid recording of eligibility assessment. Data from eligible studies will then be extracted directly into Google Sheets by one reviewer and checked by two further reviewers.

Selection Process

One reviewer will screen the title and abstracts of the studies collected according to the eligibility criteria.

One reviewer will review the full text of the studies that were deemed eligible at the abstract and title stage and select those eligible for inclusion in the analysis according to the eligibility criteria. Checking eligibility with two other reviewers.

One reviewer will extract data from the studies eligible for analysis.

We will present a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow-chart of our study selection process.[20,21]

Data items

Year of publication
Trial Population
Reference Population
Intervention(s)
Outcome(s)
A priori/ posteriori
Statistics
Model used to estimate propensity score (or alternative method)
Propensity score (or alternative method) variables
Selection procedure for propensity score (or alternative method)
Propensity score (or alternative method) analysis
Generalisability
Conclusion (unadjusted or adjusted estimate)

Risk of bias in individual studies

No formal, pre-specified assessment of methodological quality will take place. Following Gentles,[20] bias in a methodological review could be a formal logical consequence of the proposed method explicated in the narrative synthesis. Therefore, the appraisal of the strengths and weaknesses of the methodologies - rather than particular studies - is part of the analytical remit of the review.

Synthesis

A narrative synthesis will involve the generation of a list of principles and practices for statistical methods used to assess the external validity of randomised controlled trials. The reviewers will create their own interpretation of the strengths and limitations of methodologies and these interpretations will be discussed with the review team. As this is a review of methods no statistical synthesis will be conducted.

1. Yates, F. & Cochran, W. G. The analysis of groups of experiments. *J. Agric. Sci.* **28**, 556–580 (1938).
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3. Oortwijn, W., Sampietro-Colom, L. & Trowman, R. How to Deal with the Inevitable: Generating Real-World Data and Using Real-World Evidence for HTA Purposes – From Theory to Action. *Int. J. Technol. Assess. Health Care* **35**, 346–350 (2019).
4. Cobham, A. *The Uncounted*. (Polity, 2020).
5. Kennedy-Martin, T., Curtis, S., Faries, D., Robinson, S. & Johnston, J. A literature review on the representativeness of randomized controlled trial samples and implications for the external validity of trial results. *Trials* **16**, 495 (2015).
6. He, Z. *et al.* Clinical Trial Generalizability Assessment in the Big Data Era: A Review. *Clin. Transl. Sci.* **13**, 675–684 (2020).
7. Collins, J. F., Williford, W. O., Weiss, D. G., Bingham, S. F. & Klett, C. J. Planning patient recruitment: Fantasy and reality. *Stat. Med.* **3**, 435–443 (1984).
8. du Vaure, C. B., Dechartres, A., Battin, C., Ravaud, P. & Boutron, I. Exclusion of patients with concomitant chronic conditions in ongoing randomised controlled trials targeting 10 common chronic conditions and registered at ClinicalTrials.gov: a systematic review of registration details. *BMJ Open* **6**, e012265 (2016).
9. Ruiter, R., Burggraaf, J. & Rissmann, R. Under-representation of elderly in clinical trials: An analysis of the initial approval documents in the Food and Drug Administration database. *Br. J. Clin. Pharmacol.* **85**, 838–844 (2019).
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versus efficacy/effectiveness trials: a systematic review and meta-analysis. *Int. J. Behav. Nutr. Phys. Act.* **17**, 1–20 (2020).

12. Abbasi, J. Older Patients (Still) Left Out of Cancer Clinical Trials. *JAMA* (2019) doi:10.1001/jama.2019.17016.
13. Ayaz-Shah, A. A., Hussain, S. & Knight, S. R. Do clinical trials reflect reality? A systematic review of inclusion/exclusion criteria in trials of renal transplant immunosuppression. *Transpl. Int.* **31**, 353–360 (2018).
14. McClelland, S., 3rd & Mitin, T. The Danger of Applying the ProtecT Trial to Minority Populations. *JAMA Oncol* **4**, 291 (2018).
15. Eke, A. C., Dooley, K. E. & Sheffield, J. S. Pharmacologic Research in Pregnant Women - Time to Get It Right. *N. Engl. J. Med.* **380**, 1293–1295 (2019).
16. Sochacki, K. R., Jack, R. A., II, Safran, M. R., Nho, S. J. & Harris, J. D. There Is a Significant Discrepancy Between 'Big Data' Database and Original Research Publications on Hip Arthroscopy Outcomes: A Systematic Review. *Arthroscopy* **34**, 1998–2004 (2018).
17. Nelson, M. L. A. *et al.* Stroke rehabilitation evidence and comorbidity: a systematic scoping review of randomized controlled trials. *Top. Stroke Rehabil.* **24**, 374–380 (2017).
18. Reyes, C. *et al.* Real-Life and RCT Participants: Alendronate Users Versus FITs' Trial Eligibility Criterion. *Calcified Tissue International* vol. 99 243–249 (2016).
19. Hansen, B. M., Ullman, N., Norrving, B., Hanley, D. F. & Lindgren, A. Applicability of Clinical Trials in an Unselected Cohort of Patients With Intracerebral Hemorrhage. *Stroke* **47**, 2634–2637 (2016).
20. Gentles, S. J., Charles, C., Nicholas, D. B., Ploeg, J. & McKibbon, K. A. Reviewing the research methods literature: Principles and strategies illustrated by a systematic overview of sampling in qualitative research. *Syst. Rev.* **5**, 172 (2016).

21. Moher, D., Liberati, A., Tetzlaff, J. & Altman, D. G. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* **6**, e1000097 (2009).